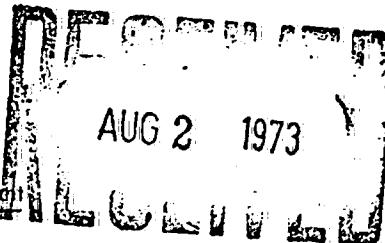


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THE COUNCIL FOR TOBACCO RESEARCH - U.S.A., INC.

110 EAST 59TH STREET
NEW YORK, N.Y. 10022
(212) 421-8885



Application For Renewal of Research Grant

(Use extra pages as needed)

First Renewal

Second Renewal

Date: July 26, 1973

1. Principal Investigator (give title and degrees):

Paul Hamosh, M.D., Assistant Professor of Physiology and Biophysics and Medicine, Georgetown University School of Medicine

2. Institution & address:

Georgetown University School of Medicine
3900 Reservoir Road, N.W.
Washington, D.C. 20007

3. Department(s) where research will be done or collaboration provided:

Department of Physiology and Biophysics, and Pulmonary Division,
Georgetown University School of Medicine

4. Short title of study:

The Effect of Smoking on the "Small Airways"

5. Proposed renewal date: January 1, 1974

6. How results to date have changed earlier specific research aims:

Earlier specific aims have not been changed. Our own data and recent observations by Bouhuys et al. (1) reinforce the validity of the specific aims: it still remains the demonstration of "reactors" and "non-reactors" to tobacco smoke. The Respiratory Diseases Task Force Report of the National Heart and Lung Institute (2) also essentially subscribes to the approach taken by our proposal.

7. How results to date have changed earlier working hypothesis:

The working hypothesis remains the same, i.e. the existence of two groups of subjects, one group predisposed to develop airway disease from tobacco smoke, whereas the second group is impervious to smoke and "protected" from airway disease. Our first working hypothesis intimated that the difference might be in the innervation of the airways and possible differential innervation of the large airways versus the small airways. Some of our observations are

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7 (continued)

appended (Da Silva, Angelo M.T. and Hamosh, Paul. The effect of smoking a single cigarette on the small airways. J. Appl. Physiol. 34:361-65, 1973). Further study along these lines is warranted especially in view of Bouhuys et al.'s finding (1). However, it would be unwise to postulate that all differences might be due to variations in innervation. Biochemical and immunological components play an equally important, or maybe even more important role. We have recently decided to test the effect of tobacco smoke on metabolism of connecting tissue and surfactant and to quantitate the morphological changes (see pre-proposal by Dr. B. Vidic).

In addition, we discovered the need to add to our protocol the study of regional distribution of inspired gases before and after smoking a cigarette. We wish to introduce ventilatory scans using Xenon¹³³. We developed for this purpose a method enabling us to scan one whole lung and divide it into regions by using a computer technique known as pattern recognition. This consists of electronic scanning of sequential Anger camera slides by a computer (IBM 360/44) connected scanner.

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8. Any additional facilities now required? Describe briefly:

a. In order to improve the quality of our maximum expiratory flow volume curves and especially eliminate the effect of thoracic gas compressions, we would prefer to switch from the present method we use, i.e. the integration of flow to volume from a spirometer (Cardio-Pulmonary Instruments, Co., Model 220) to a Mead-type volume displacement plethysmograph using an electronic circuitry manufactured by Lexington Co.

b. For the safer and more efficient handling of Xenon ¹³³ techniques we will need modification of a spirometer.

9. Any changes in personnel? Append biographical sketches of new key professional personnel:

Unfortunately we were unable to hire a pulmonary physiology technician with experience even after strenuous efforts at attracting such a person. (It is increasingly difficult to compete with laboratories delivering clinical service who pay a much more attractive salary and provide a permanent job.) Our present technician whom we had to train from scratch is leaving in September after being admitted to medical school. We have to make a new effort to attract a well-qualified technician and the salary should be commensurate to it.

10. Append outline of experimental protocol for ensuing year.

11. List publications or papers in press resulting from this or closely related work. (append reprints or manuscripts not previously sent).

- a. Da Silva, A.M.T. and Hamosh, P. The effect of smoking a single cigarette on the small airways. J. Appl. Physiol. 34:361-365, 1973.
- b. Hamosh, Paul and Da Silva, Angelo M.T. Postural hypoxemia and erythrocytosis due to airway closure at low lung volumes. Am. J. Med. 55:80-85, 1973.
- c. Hamosh, Paul and Da Silva, Angelo M.T. Determination of "closing volume" by using a bolus of room air. Submitted for publication, J. Appl. Physiol. (see appended manuscript).*

* This should be treated as confidential material, since it has not yet been acted upon by the editors.

12. Summary progress report (append in standard form as separate document, unless recently submitted)

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2a.

10. The protocol now in use is appended on the following pages. On its completion, a new protocol investigating the effect of cigarette smoke on regional ventilation will go into effect. The method for studying regional ventilation with a very small amount of inhaled Xenon¹³³ has been recently developed by us and it is under trial. Submitting a detailed protocol at this time would be premature.

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The Dose Dependence of Small Airway Function From Cigarette Smoking

Subjects: Chronic smokers able to "chain smoke" 3 cigarettes in rapid succession without getting "sick" (malaise and tachycardia).

Projected Number of Subjects: 8-12

Methods: The subjects will refrain from smoking for 2 hours before the testing. All testing should be done roughly at the same time of the day. Subjects will have to return 3 times, since only a small number of tests can be performed repeatedly within a limited time span.

1st Series: The following tests will be performed before smoking the first cigarette:

- 1) Thoracic gas volume
- 2) Airway resistance
- 3) Partial expiratory flow volume curve from 50% vital capacity
- 4) Maximum expiratory flow volume curve

These studies are to be repeated after the 1st, 2nd and 3rd cigarettes and then 1 hour following the last cigarette.

2nd Series: The general approach is as above. The following tests will be made:

- 1) An 8-breath nitrogen washout with controlled tidal volume
- 2) "Closing Volume" with bolus method
- 3) Helium partial expiratory flow volume
- 4) Helium maximum expiratory flow volume curve

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3rd Series: The following tests will be made:

- 1) "End tidal" forced expiratory volume at one second (FEV₁)
- 2) Vital capacity
- 3) FEV_{0.75}, FEV_{1.0}
- 4) MMFR
- 5) MTF
- 6) MVV

4th Series: Selected patients, where warranted, will undergo determination of frequency dependence of compliance and determination of static recoil before and after cigarette smoking.

All subjects will be volunteers from faculty and student ranks.

The procedure is entirely non-invasive and does not pose the slightest risk for the participants.

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12. Summary Progress Report

This progress report covers the period between January 1, 1973 and July 15, 1973.

a. General: This was a completely new project submitted at a time when the principal investigator changed his affiliation and had to establish a laboratory for investigation of pulmonary physiology from scratch; progress should be viewed in that light.

b. Recruitment of personnel: Mr. Mark Tanker was hired as technician February 1, 1973. He graduated from college with a major in biology. We trained him and presently he is capable of executing all the tests which are part of our protocol.

Mrs. Carole Martin who also worked in the past with us was hired as part-time secretary.

c. Facilities: We have established an all-round pulmonary function laboratory. We have done this mainly from three sources:

(1) Equipment belonging to us through the courtesy of the Veterans Administration with which organization we remain to be affiliated;

(2) From grants provided by the institution mainly with teaching as the primary purpose;

(3) From monies provided by the Council for Tobacco Research and other granting agencies.

d. Experimental Data: Since actual data gathering started only in mid-April obviously the results are not significant at present to draw firm conclusions.

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(1) The Maximum Expiratory Flow Volume (MEFV) curve: We have extended our observations that the mid-section of the MEFV curve is depressed after smoking a cigarette. We have some preliminary observations that this effect might be dose-dependent, i.e. smoking several cigarettes in succession will further decrease the mid-expiratory portion (MEF_{50} of the MEFV curve). We have also started experimenting with Partial Expiratory Flow Volume (PEFV) curves where the subject is inhaling to 60% of vital capacity and then the PEFV curve is analyzed. There is some evidence at present that the PEFV curve might be a more useful index than the MEFV curve.

(2) In the constant search for less complicated and invasive methods we have explored the total respiratory resistance method by the forced oscillation technique as a substitute for the determination of airway resistance by body plethysmography and found that this method indeed is as sensitive to the acute effect of smoking as is airway resistance determined by body plethysmography. We also explored in a number of subjects the "end-tidal" forced expiratory volume presented recently by Dr. Lim at the Federation of American Societies for Experimental Biology meeting (3). This method shows great promise and might ultimately supplant MEF_{50} as a rapid and simple screening method capable of using simple spiroometry rather than sophisticated flow-volume tracings.

(3) We have done further work on closing volumes (see appendix). This measurement as performed by the single breath nitrogen washout proved to be not sensitive enough to pick up

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subtle changes after smoking a cigarette. We have devised a bolus method which enhances the resolution of phase IV of closing volume method. The standard error of estimate is much lower with this method, and we hope to be able to detect small changes with a sufficient degree of reliability.

(4) We have applied for the use of blocking agents and marihuana to explore their interaction with tobacco smoke and to use them in "provocation" tests (see original application).

In Summary: Considering the short time available until presentation of this report we have:

- a. Significantly improved and simplified our methodology;
- b. Obtained some preliminary results suggesting the correctness of our working hypothesis;
- c. Developed new methods for testing closing volume and regional ventilation.

REFERENCES:

- (1) C.A. Mitchell, E. Zuskin and A. Bouhuys. The effect of cigarette smoke and β -adrenergic antagonists on small airways. Abstract presented at Annual Meeting of American Thoracic Society, May 21-23, 1973.
- (2) Respiratory Diseases: Task Force Report on Problems, Research Approaches and Needs. The Lung Program, National Heart and Lung Institute, 1972. DHEW Publication No. (NIH) 73-432.
- (3) Thomas P.K. Lim. Detection of early airway obstruction. Fed. Proc. 32:415 (abs), 1973.

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Remarks Pertaining to Budgetary Changes

This budget is higher than the projected one and is about at the level of the first year funding. The increase is due to:

1. An unanticipated need to stipulate partial salary for the principal investigator as a result of changing academic realities (\$2,600);
2. The unexpected increase in salary requirements for qualified personnel (\$2,500 over projected);
3. An increase in the cost of supplies (\$500) because of galloping inflation;
4. An increase in the other expenses (\$500) due to increased cost of publication and cost of other related services;
5. \$4,000 for permanent equipment consisting mostly of electronics and modifications of existing equipment to give us the capability of expanding into new areas of methodology required by recent discoveries in the field.

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13. Budget for the coming year:

A. Salaries (give names or state "to be recruited")

Professional (give % time of investigator(s)
even if no salary requested)

Paul Hamosh, M.D.*

% time

Amount

10

\$2,942 (10%)

Hall G. Canter, M.D.

5

none

Technical *

Research Assistant (Pulmonary
Technician) to be hired

100

\$12,000.

Carole Martin (Secretary)

40

2,658

* Including 11% fringe benefits

Sub-Total for A

\$17,600.

B. Consumable supplies (by major categories)

Gases, chemicals etc.

1,000.

Recording paper, radioactive gases

500.

Sub-Total for B

1,500.

C. Other expenses (itemize)

Travel

750.

Publications

500.

Computer time (data processing)

250.

Consultation (electronics)

500.

Sub-Total for C

2,000.

Running Total of A + B + C

21,100.

D. Permanent equipment (itemize)

Special electronics for volume plethysmograph
(Lexington Co.)

2,500.

Modification of spirometer for Xenon ¹³³ work
(to be incorporated as permanent equipment)

1,500.

Sub-Total for D

4,000.

E. Indirect costs (15% of A+B+C)

E

3,165.

Total request

\$28,265.

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14. Other sources of financial support:

→ List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
1. Surfactant metabolism as a function of ventilation	Washington Heart Assoc. 3287-785	\$7528.	1/1/73 - 12/31/73
2. Effect of mechanical stress on the elastic properties of the lung in papain induced emphysema	GRS-NIH 3302-113 (through own institution)	\$2500.	1/1/73 - 12/31/73
3. Quantitation of lung cancer on chest films by computer	Contract with the Veterans Administration	\$10,800.	1/1/73 - 12/31/73

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
1. Computerized Chest X-ray followup in cancer therapy	National Cancer Institute	\$80,460.	1/1/74 - 12/31/76
2. Pediatric lung development program project	National Heart and Lung Institute	approx. 200,000.	7/1/74 - 6/30/79

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Paul Hamosh, M.D.

Signature P. Hamosh Date 7/26/73

(202) 625-7548

Telephone _____ Area Code _____ Number _____ Extension _____

Responsible officer of institution

Typed Name Guerry R. Smith

Title Acting Administrator, Sponsored Programs

Signature Guerry R. Smith Date 7/31/73

(202) 625-3151

Telephone _____ Area Code _____ Number _____ Extension _____

Checks payable to

Georgetown University

Mailing address for check: Sam A. Kimble
Georgetown University
37th and O Streets, N.W.
Washington, D.C. 20007

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